

Importance of Infarct-Related Artery Patency for Recovery of Left Ventricular Function and Late Survival After Primary Angioplasty for Acute Myocardial Infarction

BRUCE R. BRODIE, MD, FACC, THOMAS D. STUCKEY, MD, FACC, GRACE KISSLING, PhD,*
CHARLES J. HANSEN, MA, RICHARD A. WEINTRAUB, MD, FACC,
THOMAS A. KELLY, MD, FACC

Greensboro, North Carolina

Objectives. The purpose of this study was to evaluate the importance of late infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction.

Background. Infarct-related artery patency is thought to improve late survival by its effect on preservation of left ventricular function. Patency may also enhance late survival by preventing left ventricular dilation and reducing arrhythmias, independent of myocardial salvage. However, most studies have not shown patency to be an independent predictor of survival when late left ventricular function is taken into account.

Methods. We followed up 576 hospital survivors of acute myocardial infarction treated with primary angioplasty for 5.3 years. Ejection fraction and infarct-related artery patency were determined at follow-up catheterization at 6 months. Predictors of late cardiac survival were determined using Cox regression models.

Results. Patients with patent arteries had more improvement and a better late ejection fraction than patients with occluded

arteries (56.3% vs. 47.9%, $p = 0.001$). In patients with acute ejection fraction $<45\%$, late survival was better in those with patent versus occluded arteries (89% vs. 44%, $p = 0.003$), but patency was not a significant predictor after improvement in ejection fraction was taken into account. In patients with a large anterior infarction, patency was a significant independent predictor of late survival.

Conclusions. Infarct-related artery patency is important for recovery of left ventricular function, and in patients with acute ejection fraction $<45\%$, patency is important for late survival. Our data are consistent with the hypothesis that the survival benefit is due primarily to the effect of patency on recovery of left ventricular function. In patients with a large anterior infarction, patency appears to provide an additional late survival benefit independent of myocardial salvage. These observations support the need for additional clinical trials of late reperfusion in patients with a large anterior infarction.

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Myocardial reperfusion has been shown to improve both short- and long-term survival in acute myocardial infarction (1,2). Although this has been thought to be related primarily to the effects of reperfusion on preservation of left ventricular function, several observations suggest that reestablishing patency of the infarct-related artery may have benefits independent of myocardial salvage (2-5). Possible mechanisms for this benefit include prevention of left ventricular dilation (6,7), improvement in electrical stability (8,9) and providing a conduit for collateral flow in the event of occlusion of a contralateral coronary artery (4,5).

From the Department of Medicine, Moses H. Cone Memorial Hospital and LeBauer Cardiovascular Research Foundation and *Department of Mathematical Sciences, Division of Statistics, University of North Carolina at Greensboro, Greensboro, North Carolina. This study was supported by a grant from the LeBauer Cardiovascular Research Foundation.

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Address for correspondence: Dr. Bruce R. Brodie, 520 North Elam Avenue, Greensboro, North Carolina 27401.

Several studies of thrombolytic therapy have shown that infarct-related artery patency is a univariate predictor of late cardiac survival, but most studies have either not measured late left ventricular function or have not shown infarct-related artery patency to be an independent predictor of late survival when late left ventricular function was taken into account (3,10,11).

The purpose of the present study was to evaluate the importance of infarct-related artery patency for late cardiac survival after direct angioplasty for acute myocardial infarction and to determine whether patency improves late survival through its effect on recovery of left ventricular function or whether there is a beneficial effect that is independent of myocardial salvage.

Methods

Study subjects. From 1984 through 1991, 633 consecutive patients with an acute myocardial infarction and a diagnostic electrocardiogram (ECG) who were treated with primary

angioplasty without prior thrombolytic therapy were prospectively entered into an ongoing data base. Diagnostic ECGs were defined as ST segment elevation ≥ 1 mm in two or more contiguous leads, reciprocal ST segment depression ≥ 1 mm in leads V_1 to V_2 or left bundle branch block. Patients were not treated with primary angioplasty if they had severe comorbid disease or presented >12 h after the onset of infarction. Primary angioplasty is the preferred reperfusion strategy at our institution, where $\sim 77\%$ of patients with a diagnostic ECG have undergone acute catheterization, and 70% have been treated with primary angioplasty (12). Of the 633 patients treated with primary angioplasty, there were 576 hospital survivors who comprise our study population.

Treatment protocol. Patients presenting to the emergency department were given 10,000 U of heparin and chewable aspirin and transported promptly to the cardiac catheterization laboratory. Cardiac catheterization was performed, and coronary reperfusion was established mechanically with primary angioplasty as previously described (13). Patients were treated with intravenous heparin for 3 to 5 days to prolong the partial thromboplastin time to 60 to 80 s. Aspirin was given routinely, and beta-adrenergic blocking drugs and nitrates were given at the discretion of the attending physician. Reinfarction and recurrent ischemia were treated when appropriate with repeat angioplasty or coronary bypass surgery in an attempt to maintain patency of the infarct-related artery.

Follow-up catheterization and angiography. Follow-up catheterization and angiography were performed routinely for the first 3 years of the study and for an 18-month period from 1990 to 1991 during follow-up of the Primary Angioplasty Registry (14). Otherwise, follow-up catheterization was performed for recurrent ischemic symptoms or abnormal functional testing. Follow-up catheterization was performed in 374 (65%) of 576 patients at a median follow-up time of 5.6 months. In 316 of these studies (55% of all patients), left ventricular cineangiograms were adequate for calculation of follow-up ejection fraction. Left ventricular ejection fractions were calculated from tracing contours of right anterior oblique cineangiograms using the area-length method with correction for the right anterior oblique projection (15). In 10 patients who died after hospital discharge without follow-up angiography, follow-up left ventricular ejection fraction measured by radionuclide ventriculography was used in the analysis.

Clinical follow-up. Clinical follow-up was obtained by hospital and office chart review and telephone contact. Events recorded included death, cause of death, reinfarction, repeat angioplasty and bypass surgery. Complete follow-up was obtained in 565 (98%) of 576 patients at a median follow-up time of 5.3 years.

Data analysis. Variables examined as predictors of late cardiac survival included age, gender, prior myocardial infarction, prior coronary bypass surgery, cardiogenic shock before intervention, infarct location, multivessel coronary artery disease, acute left ventricular ejection fraction, late (follow-up) ejection fraction, improvement in ejection fraction and infarct-related artery patency.

Infarct-related artery patency was determined at follow-up catheterization in 374 (65%) of 576 patients. The infarct artery was considered patent at follow-up angiography if the flow was Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 (339 patients). In patients who did not have follow-up catheterization, the infarct artery was considered patent if the initial primary angioplasty procedure was successful and there was no reinfarction (182 patients) or, in the case of patients with unsuccessful angioplasty, if the patient underwent coronary artery bypass surgery during the initial hospital period (7 patients). The infarct artery was considered occluded at follow-up angiography if the flow was TIMI grade 0 or 1 (35 patients). In patients who did not have follow up angiography, the infarct artery was considered occluded if the angioplasty procedure was unsuccessful (10 patients) or if there was reinfarction without repeat revascularization (3 patients).

Comparisons of baseline variables between subgroups were performed using the chi-square statistic and Student two-tailed *t* tests. Differences in late cardiac survival across categories of discrete predictor variables were examined with Kaplan-Meier survival curves and their associated log-rank test statistics. Multivariable analyses of predictors of late cardiac survival were performed using Cox proportional hazards regression models. A stepwise selection method was used with an inclusion criteria of a *p* value ≤ 0.10 . Only patients with patency documented at follow-up angiography and paired ejection fraction data were included in multivariable analyses that evaluated improvement in ejection fraction or late ejection fraction as potential predictor variables. All analyses were performed with SAS and SPSS statistical software.

Results

Of 633 patients treated with primary angioplasty, 57 died in the hospital, and 576 survived the hospital period. Reperfusion with angioplasty was successful in 595 patients (94%). Coronary artery bypass surgery was performed during the hospital period in 44 patients (7.0%) and repeat angioplasty of the infarct-related artery in 25.

Baseline characteristics. The baseline characteristics of the 576 hospital survivors are shown in Tables 1 and 2. Patients with follow-up angiography were younger and had a lower incidence of cardiogenic shock, a higher incidence of anterior infarction and a lower acute mean ejection fraction than patients without follow-up angiography (Table 1). Patients with a patent infarct-related artery had fewer prior infarctions and more multivessel disease than patients with occluded arteries (Table 2).

Late follow-up. The 576 hospital survivors were followed up for a median of 5.3 years. There were 37 late noncardiac and 48 late cardiac deaths (28 sudden deaths). The late infarct artery patency rate in patients with follow-up angiography was 91%.

Predictors of late cardiac survival. Kaplan-Meier survival curves for selected predictor variables are shown in Figure 1. Significant univariate predictors of late survival by the log-rank

Table 1. Baseline Characteristics of 576 Patients Discharged From Hospital After Primary Angioplasty for Acute Myocardial Infarction With and Without Follow-Up Angiography

	Follow-Up Angiography (n = 374)	No Follow-Up Angiography (n = 202)	All Pts (n = 576)
Age (yr)	57 ± 11*	61 ± 11	58 ± 11
Women	95 (25)	52 (26)	147 (26)
Prior MI	63 (17)	46 (23)	109 (19)
Prior CABG	13 (3.5)	7 (3.5)	20 (3.5)
Cardiogenic shock	15 (4.0)†	18 (8.9)	33 (5.7)
Ant MI	172 (46)*	70 (35)	242 (42)
Multivessel CAD	195 (52)	104 (52)	299 (52)
Reperfusion time (h)	4.1 ± 3.3	4.3 ± 3.3	4.2 ± 3.3
Acute EF (%)	52.2 ± 13*	55.6 ± 12	53.4 ± 13

*p < 0.01, †p < 0.05 versus patients (Pts) with no follow-up angiography. Data presented are mean value ± SD or number (%) of patients. Ant = anterior; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; EF = ejection fraction; MI = myocardial infarction.

test were acute ejection fraction (p = 0.002), late ejection fraction (p < 0.001), improvement in ejection fraction (p < 0.001), prior coronary bypass surgery (p < 0.001) and multivessel coronary disease (p = 0.008). Survival curves were not significantly different in patients with a patent versus an occluded infarct-related artery (p = 0.43).

Multivariable predictors of late cardiac survival in a Cox proportional hazards model are shown in Table 3. When acute ejection fraction was included in the model (model 1), significant predictors of late cardiac survival were acute ejection fraction (p = 0.01), prior bypass surgery (p = 0.01) and infarct-related artery patency (p = 0.03). When improvement in ejection fraction was added to the model (model 2), significant predictors were improvement in ejection fraction (p < 0.0001), acute ejection fraction (p = 0.0003), prior bypass surgery (p = 0.01) and gender (p = 0.03); infarct artery patency was no longer a significant predictor. When late ejection fraction was included in the model (model 3), significant predictors were late ejection fraction (p < 0.0001), prior

Table 2. Baseline Characteristics in 576 Patients According to Infarct-Related Artery Patency

	Patent IRA (n = 528)	Occluded IRA (n = 48)	p Value
Age (yr)	58 ± 11	58 ± 12	NS
Women	132 (25)	15 (31)	NS
Prior MI	95 (18)	14 (29)	0.06
Prior CABG	18 (3.4)	2 (4.2)	NS
Cardiogenic shock	30 (5.7)	3 (6.3)	NS
Ant MI	224 (42)	18 (38)	NS
Multivessel CAD	282 (53)	17 (35)	0.02
Reperfusion time (h)	4.2 ± 3.3	4.2 ± 3.5	NS
Acute EF (%)	53.5 ± 13	52.1 ± 11	NS

Data presented are mean value ± SD or number (%) of patients. IRA = infarct-related artery; other abbreviations as in Table 1.

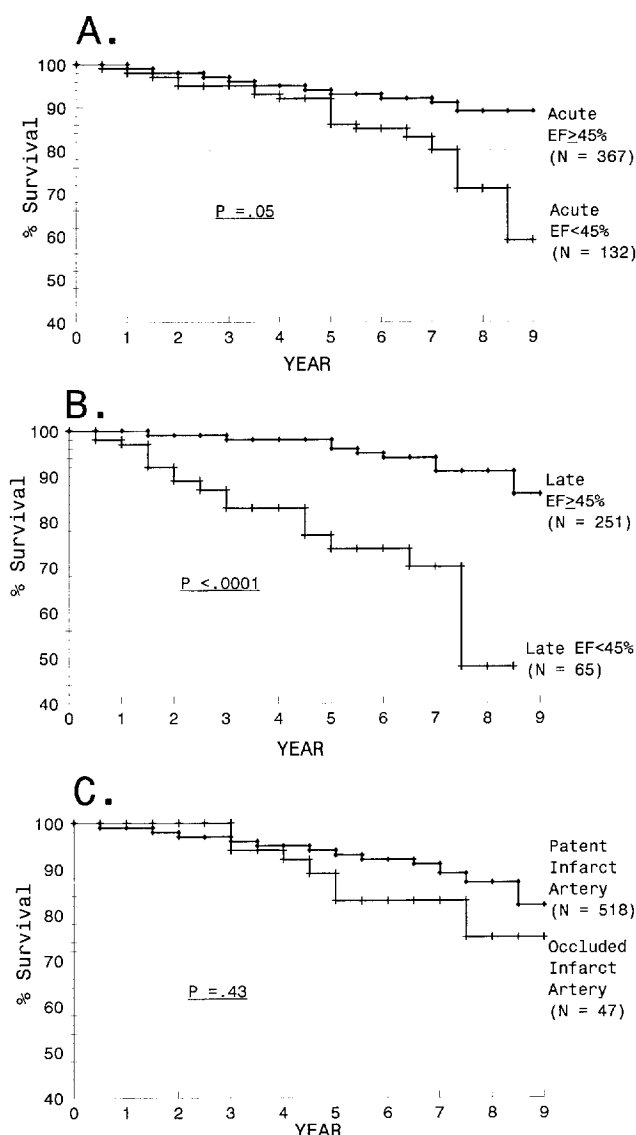


Figure 1. Kaplan-Meier cardiac survival curves after primary angioplasty for acute myocardial infarction comparing three predictor variables: **A**, acute ejection fraction (EF) ≥45% versus <45%; **B**, late ejection fraction ≥45% versus <45%; **C**, patent versus occluded infarct-related arteries at follow-up.

bypass surgery (p = 0.01) and gender (p = 0.04); patency was not a significant predictor.

Effect of infarct-related artery patency on recovery of left ventricular function. Acute and follow-up left ventricular ejection fraction in patients with paired data are shown in Figure 2 and Table 4. Patients with a patent versus an occluded infarct-related artery had more improvement in ejection fraction (4.9% vs. -3.4%, p < 0.0001) and a higher follow-up ejection fraction (56.3% vs. 47.9%, p = 0.001). These differences were also true within each subgroup evaluated (Table 4).

Effect of infarct-related artery patency on late cardiac survival in subgroups. The correlation between infarct-related artery patency and late cardiac survival in the subgroups is shown in Figure 3 and Table 5, and the results of the

Table 3. Cox Regression Models for Late Cardiac Survival*

Variable	All Patients				Acute EF <45%				Ant MI With Acute EF <45%			
	Model 1 (n = 499)	Model 2 (n = 302)	Model 3 (n = 302)	Model 4 (n = 132)	Model 5 (n = 98)	Model 6 (n = 98)	Model 7 (n = 88)	Model 8 (n = 69)	Model 9 (n = 69)	Beta	p	Value
Age	NS†	NS†	NS†	0.054	0.049	NS†	0.094	0.006	0.109	0.111	0.007	0.007
Women	NS†	0.853	0.03	NS†	NS†	NS†	NS†	NS†	NS†	NS†	NS†	NS†
Prior CABG	1.403	1.544	0.01	1.74	NS†	1.602	NS†	NS†	2.545	2.288	NS†	NS†
Patent IRA	0.342	NS†	NS†	0.708	0.406	NS†	3.307	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Acute EF	-0.034	-0.055	0.0003	NS†	NS†	NS†	-0.107	0.04	-0.110	0.05	NS†	NS†
Improvement in EF	—	-0.087	<0.0001	—	-0.065	0.001	—	—	-0.048	0.08	—	—
Late EF	—	—	-0.071	—	—	-0.081	—	—	—	-0.054	—	0.02

*Multivessel coronary disease, prior myocardial infarction and anterior myocardial infarction were available for selection in all models but were not significant predictors; positive coefficients are associated with increased mortality for dichotomous variables listed; negative coefficients for acute ejection fraction, improvement in ejection fraction and late ejection fraction indicate increasing mortality associated with decreasing ejection fraction. †p > 0.10 (criteria for stepwise selection not met for inclusion in model). Abbreviations as in Tables 1 and 2; — = variables not considered for the model.

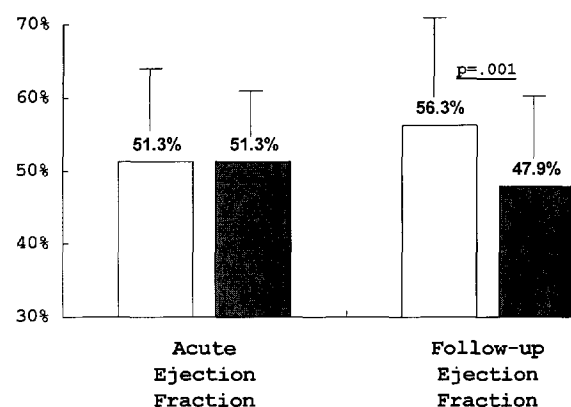


Figure 2. Acute and follow-up ejection fraction (mean \pm SD) after primary angioplasty for acute myocardial infarction in patients with a patent versus occluded infarct-related artery (paired ejection fraction data). Patients with a patent artery had a significantly higher follow-up ejection fraction than did patients with occluded arteries. **Open bars** = patent infarct-related artery (n = 271); **gray bars** = occluded infarct-related artery (n = 31).

multivariable analyses are shown in Table 3. In patients with an acute ejection fraction $\geq 45\%$, patency was not a significant univariate predictor of late cardiac survival (Fig. 3, Table 5). In patients with an acute ejection fraction $< 45\%$, patency was a strong univariate predictor of late survival (Fig. 3, Table 5) and was the strongest predictor of late cardiac survival in a multivariable model that included acute left ventricular ejection fraction (before recovery of left ventricular function) (model 4, Table 3). When late ejection fraction (reflecting recovery of left ventricular function) was added to the model, patency did not reach significance as an independent predictor (model 6, Table 3).

In patients with an anterior infarction, patency was a strong univariate predictor of late survival (Fig. 3, Table 5) and was the strongest predictor of late cardiac survival in a multivariable model that included acute ejection fraction. When improvement in ejection fraction or late ejection fraction (reflecting recovery of left ventricular function) was included in the model, patency was no longer a significant predictor of late survival.

In patients with an anterior infarction and acute ejection fraction $< 45\%$, patency was a significant independent predictor of late cardiac survival in multivariable models that included improvement in ejection fraction or late ejection fraction (models 8 and 9, Table 3). Among the patients with a non-anterior-wall infarction and acute ejection fraction $\leq 45\%$, there were only two with occluded arteries, so no meaningful statistical comparisons could be made in this subgroup.

Discussion

Our study confirms that in the reperfusion era, left ventricular function remains the most important determinant of late cardiac survival. Infarct-related artery patency is important for recovery of left ventricular function, and in patients with an

Table 4. Relation Between Infarct-Related Artery Patency and Left Ventricular Ejection Fraction in Patients With Paired Ejection Fraction

	Patent IRA (mean \pm SD)	Occluded IRA (mean \pm SD)	p Value
All pts (n = 302 [patent 271, occluded 3])			
Acute EF (%)	51.3 \pm 12	51.3 \pm 10	NS*
Follow-up EF (%)	56.3 \pm 14	47.9 \pm 12	0.001
Improvement EF (%)	4.9 \pm 11	-3.4 \pm 10	0.0001
Acute EF \geq 45% (n = 204 [patent 181, occluded 23])			
Acute EF (%)	58.5 \pm 9	56.6 \pm 7	NS*
Follow-up EF (%)	61.6 \pm 10	50.7 \pm 9	<0.0001
Improvement EF (%)	3.1 \pm 10	-5.9 \pm 6	<0.0001
Acute EF <45% (n = 98 [patent 90, occluded 8])			
Acute EF (%)	36.9 \pm 7	36.3 \pm 4	NS*
Follow-up EF (%)	45.5 \pm 15	40.0 \pm 17	NS*
Improvement EF (%)	8.6 \pm 13	3.8 \pm 16	NS*
Ant MI (n = 140 [patent 128, occluded 12])			
Acute EF (%)	45.5 \pm 12	45.8 \pm 10	NS*
Follow-up EF (%)	53.7 \pm 16	43.8 \pm 13	0.03
Improvement EF (%)	8.2 \pm 12	-2.0 \pm 11	0.008
Non-Ant MI (n = 162 [patent 143, occluded 19])			
Acute EF (%)	56.6 \pm 12	54.8 \pm 10	NS*
Follow-up EF (%)	58.6 \pm 12	50.5 \pm 11	0.008
Improvement EF (%)	2.0 \pm 10	-4.3 \pm 10	0.02
Ant MI with acute EF <45% (n = 69 [patent 63, occluded 6])			
Acute EF (%)	36.3 \pm 7	36.8 \pm 4	NS*
Follow-up EF (%)	44.9 \pm 15	38.3 \pm 16	NS*
Improvement EF (%)	8.7 \pm 13	1.5 \pm 15	NS*

*p > 0.10. Abbreviations as in Tables 1 and 2.

anterior infarction or acute left ventricular dysfunction, patency is a strong univariate predictor of late cardiac survival. However, patency is not a significant independent predictor of late survival in these patients after improvement in left ventricular function is accounted for. In patients who have both an anterior infarction and acute left ventricular dysfunction, infarct artery patency is a significant predictor of late cardiac survival independent of its effect on recovery of left ventricular function.

Previous studies regarding importance of infarct-related artery patency for late cardiac survival. The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) (16) angiographic investigators have convincingly shown the importance of infarct-related artery patency for hospital survival. Infarct artery patency also appears to be important for late (posthospital) cardiac survival (3,10,11,17-19), but it has not been clear whether this is related to the effect of infarct artery patency on recovery of left ventricular function or whether patency has an independent effect on late survival. Several studies of thrombolytic therapy have shown that infarct artery patency is an important univariate predictor

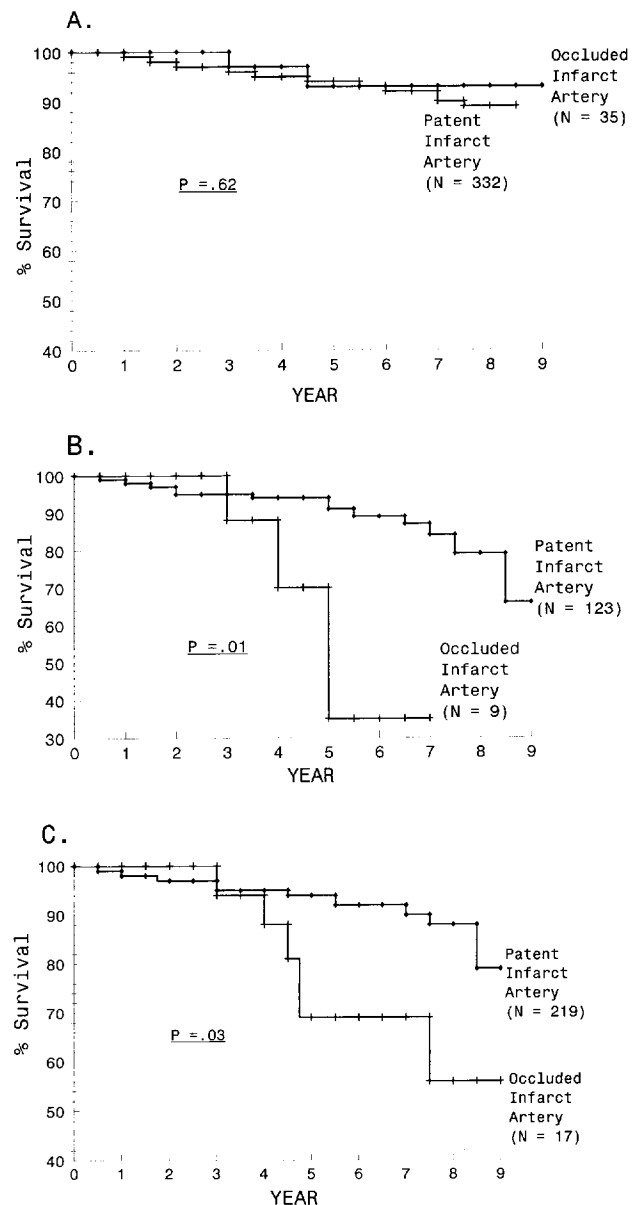


Figure 3. Kaplan-Meier cardiac survival curves after primary angioplasty for acute myocardial infarction comparing patients with a patent versus occluded infarct-related artery in three subgroups: **A**, patients with acute ejection fraction \geq 45%; **B**, patients with acute ejection fraction <45%; and **C**, patients with an anterior infarction.

of late cardiac survival (3,10,11,17,19), but most studies either have not measured late left ventricular function or have not shown infarct artery patency to be an independent predictor of late cardiac survival when late left ventricular function was included in the multivariable analyses. The Western Washington Intracoronary Streptokinase trial (3) showed that infarct artery patency was an independent predictor of late cardiac survival when acute ejection fraction was included in the analyses. However, when left ventricular ejection fraction measured at 3 days (after some recovery had occurred) was included in the multivariable analyses, infarct artery patency was no longer a significant predictor of late cardiac survival

Table 5. Relation Between Infarct-Related Artery Patency and Late Cardiac Mortality in Patient Subgroups

Variable	Patent IRA	Occluded IRA	p Value
All pts (n = 565)	40/518 (7.7)	7/47 (15)	0.09
Acute EF \geq 45% (n = 367)	23/332 (6.9)	2/35 (5.7)	NS*
Acute EF <45% (n = 132)	14/123 (11)	5/9 (56)	0.0003
Ant MI (n = 236)	18/219 (8.2)	6/17 (35)	0.0004
Non-Ant MI (n = 329)	22/299 (7.4)	1/30 (3.3)	NS*
Ant MI with acute EF <45% (n = 88)	6/81 (7.4)	5/7 (71)	<0.0001

*p > 0.10. Data presented are number of deaths/number of patients (%). Abbreviations as in Tables 1 and 2.

(20). Likewise, the Interuniversity Cardiology Institute of The Netherlands trial (11), in which patients with acute myocardial infarction were treated with intracoronary streptokinase or urokinase, found that infarct artery patency was a univariate predictor of late survival, but patency was no longer a predictor of survival when patients were stratified by ejection fraction. Both of these studies suggest that infarct artery patency improves late cardiac survival primarily by its effect on recovery of left ventricular function.

Two studies to date have suggested that infarct-related artery patency may have a beneficial effect on late cardiac survival, independent of myocardial salvage (21,22). White et al. (21) measured left ventricular function 4 weeks after infarction and found that infarct artery patency (when expressed as a variable that included the amount of myocardium supplied by the infarct artery) was an independent predictor of late cardiac survival. Infarct artery patency was most important for late survival in patients with depressed left ventricular function. Likewise, the Survival and Ventricular Enlargement (SAVE) Investigators (22) assessed infarct artery patency and left ventricular ejection fraction 4 days after infarction in patients with left ventricular dysfunction (ejection fraction <40%) and found patency to be a significant predictor of late survival after correcting for differences in left ventricular ejection fraction and other predictor variables (22).

Comparison of our results with those of previous studies. Our data support the findings of previous studies of primary angioplasty (14,23) and thrombolytic therapy (24) that late infarct-related artery patency is important for recovery of left ventricular function. In patients with a small infarction, late survival is very good, and infarct-related artery patency has very little effect on late cardiac survival. In patients with an anterior infarction or acutely depressed left ventricular function, infarct artery patency is a strong univariate predictor of late survival but is not a significant independent predictor after improvement in left ventricular function has been taken into account. This is similar to the findings of Sheehan et al. (20) and The Netherlands trial (11). However, in patients with an anterior infarction and acute left ventricular dysfunction, patency appears to have a beneficial effect on late cardiac survival that is independent of myocardial salvage. This is similar to the findings of White et al. (21) and the SAVE Investigators (22).

There are several possible mechanisms for the independent effects of infarct-related artery patency on late cardiac survival. These have been well described elsewhere and include prevention of left ventricular dilation or remodeling (6,7), improvement in electrical stability (8,9) and providing a conduit for collateral flow in the event of an occlusion of a contralateral artery (4,5).

Study limitations. Our study is limited because follow-up angiography was obtained in only 65% of patients. Patients with follow-up angiography were younger and had a higher incidence of anterior infarction and a lower acute ejection fraction than patients without follow-up angiography. Patients with an anterior infarction and a low acute ejection fraction have greater improvement in ejection fraction after successful reperfusion (23), so this could result in an overestimation of improvement in ejection fraction in our patients. Patients with a low acute ejection fraction have higher late mortality, so our analyses of patients with follow-up angiography could result in an overestimation of late mortality.

Coronary artery bypass surgery was performed before discharge in 40 hospital survivors in the patent artery group (vs. none in the occluded artery group), making it difficult to determine whether patency or bypass surgery is more important for late survival in these patients. However, late mortality was higher in patients with (15%) than without bypass surgery (7.8%), so it seems unlikely that the use of bypass surgery greatly influenced our results.

Finally, the relatively small number of late cardiac deaths and the relatively small number of patients with an occluded infarct-related artery limit our subgroup analyses.

Clinical implications. Our data confirm that late infarct-related artery patency is important for recovery of left ventricular function. In patients with a small myocardial infarction, survival is very good, and infarct artery patency has very little effect on late survival. In patients with an anterior infarction or acute left ventricular dysfunction, patency is important for late survival but is not a significant independent predictor after correction for recovery of left ventricular function. These data are consistent with the hypothesis that in patients with an anterior infarction or left ventricular dysfunction, patency improves late survival primarily by its effect on recovery of left ventricular function. In patients with an anterior infarction and acute left ventricular dysfunction, patency appears to provide an additional beneficial effect on late cardiac survival that is independent of myocardial salvage. These observations should encourage prospective studies to evaluate the survival benefit of late coronary reperfusion (when myocardial salvage is no longer expected) in patients with a large anterior infarction.

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